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EFFECTS OF COMPOUNDING DRUG-RELATED STIMULI: ESCALATION OF HEROIN SELF-ADMINISTRATION

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Previous experiments have demonstrated that presenting independently established discriminative stimuli in compound can substantially increase operant responding maintained by food reinforcement or shock avoidance. Recently, this phenomenon was also shown to occur with cocaine self-administration. The present study further assessed the generality of these stimulus-compounding effects by systematically replicating them with heroin self-administration. Rats' nose-poke responses produced intravenous heroin (0.025 mg/kg per infusion) on a variable-ratio schedule when either a tone or a light was present. In the absence of these stimuli, responding was not reinforced. Once discriminative control by the tone and light had been established, the stimuli were presented in compound under extinction (with heroin discontinued) or maintenance conditions (with heroin available during test-stimulus presentations). In extinction, the tone–light compound increased responding approximately threefold compared to tone or light alone. Under maintenance conditions, compounding increased heroin intake approximately twofold. These effects closely matched those obtained earlier with cocaine. This consistency across pharmacological classes and across drug and nondrug reinforcers further confirms that (a) self-administered drugs support conditioning and learning in a manner similar to that supported by other reinforcers; and (b) multiple drug-related cues interact in lawful and predictable ways to affect drug seeking and consumption.

Key words: self-administration, stimulus compounding, stimulus control, drug abuse, incentive-motivation, nose poke, rat

Stimulus control in the natural environment typically involves multiple stimuli that interact to influence behavior. An effective means of examining such interactions in the laboratory is to establish discriminative stimuli independently and then to present them together in a stimulus-compounding test. This stimulus-compounding paradigm has provided a number of unique insights into fundamental behavioral processes. For example, compounding procedures have been used to elucidate the independent influences of response and incentive factors in operant schedules of reinforcement (Weiss, 1978; Weiss & Schindler, 1987), and they have been used to demonstrate inhibitory interactions between the effects of appetitive and aversive reinforcers (Weiss & Schindler, 1989; Weiss, Thomas, & Weissman, 1996; Weissman, 1995). Until recently, however, compounding studies have been limited almost exclusively to behavior maintained by food reinforcement or shock avoidance.

Panlilio, Weiss, and Schindler (1996) applied a stimulus-compounding technique for the first time to behavior maintained by a drug reinforcer. A multiple schedule of reinforcement was used to establish a tone and a light as discriminative stimuli for cocaine self-administration. When either the tone or the light was present, rats' lever-press responses produced intravenous infusions of cocaine on a variable-ratio (VR) schedule. In the absence of tone or light, responding did not produce cocaine. Once the tone and light had each gained discriminative control of self-administration responding (i.e., responding tended to occur only in their presence), the stimuli were presented together during stimulus-compounding tests. When tone and light were compounded in extinction (with all cocaine delivery discontinued), response rates increased threefold compared to the rates controlled by tone or light alone. When

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drug availability was maintained during testing, the rate of cocaine intake was doubled in the presence of the compound stimulus. This enhanced responding closely replicated results obtained earlier with similar reinforcement schedules involving food (Weiss, 1964, 1969, 1971), water (Weiss, Schindler, & Easton, 1988, Experiment 1), and shock avoidance (Emurian & Weiss, 1972; Weiss, 1976).

The goal of the present study was to further extend the stimulus-compounding paradigm to a drug reinforcer that represents a different pharmacological class than cocaine. To achieve this, the study described above (Panlilio et al., 1996) was systematically replicated (Sidman, 1960) using heroin instead of cocaine as the reinforcer. Although heroin and cocaine both have powerful reinforcing effects in animals and humans (Comer et al., 1998; Yokel, 1986), they act on different physiological substrates (Chang, Janak, & Woodward, 1998; Koob, 1992; Koob, Vaccarino, Amalric, & Bloom, 1986) and exhibit different profiles of behavioral effects. For example, psychomotor stimulants such as cocaine tend to increase rates of operant responding maintained by nondrug reinforcers, whereas opioids such as heroin tend to decrease these rates (Seiden & Dykstra, 1977). Under unlimited-access conditions, heroin typically maintains stable levels of self-administration, while cocaine produces cycles of bingeing and abstinence (Bozarth & Wise, 1985). In runway studies, self-administered cocaine (but not heroin) may have both reinforcing and punishing effects that are similar to those of food combined with shock (Ettenberg & Geist, 1993; Geist & Ettenberg, 1997). Thus, cocaine and heroin appear to differ in their motivational effects and their direct effects on operant responding, two important characteristics that could influence the outcome of stimulus-compounding tests.

Stimulus control is believed to play an important role in human drug abuse by supporting the complex sequences of behavior involved in obtaining, preparing, and ingesting drugs (Bickel & Kelly, 1988; Kirby, Lamb, & Iguchi, 1997; Schindler, Katz, & Goldberg, 1988; Stewart, DeWit, & Eikelboom, 1984). It is likely that multiple drug-related cues interact to influence behavior, and the effects of a given stimulus may be altered when it is encountered in combination with other stimuli. By applying stimulus-compounding techniques to animal models of drug abuse, we can begin to understand how behavior is affected by multiple drug-related stimuli. The demonstration that stimulus compounding can substantially increase cocaine self-administration in rats (Panlilio, Weiss, & Schindler, 1996, 1998) suggests that humans exposed to multiple drug-related stimuli might go to greater lengths to obtain drugs, and they might ingest larger-than-usual quantities once the drugs are obtained. To assess the generality of this phenomenon, a logical step is to determine whether the same circumstances that increase the self-administration of cocaine can also increase the self-administration of heroin, a widely abused drug that exhibits a different profile of pharmacological and behavioral effects. If similar enhancement effects occur across a range of different drug reinforcers, the processes involved are indeed general and therefore more important than if they are restricted to a narrow range of circumstances.

METHOD

Subjects

Four experimentally naive male Sprague-Dawley rats (Charles River Laboratories) were approximately 3 months old at the beginning of the study and weighed approximately 300 to 350 g for the duration of the study. The rats were individually housed with free access to water and were fed approximately 15 g of food daily after their training sessions. Lights in the colony room were turned on at 6:00 a.m. and off at 8:00 p.m., and experiments were conducted between 12:00 p.m. and 4:00 p.m. Monday through Friday.

Jugular-vein catheters were implanted under anesthesia with ketamine (60 mg/kg) and xylazine (10 mg/kg) following procedures described in detail elsewhere (Panlilio et al., 1996). In brief, approximately 4 cm of Silastic tubing (0.44 mm inner diameter, 0.814 mm outer diameter) was inserted into the vein and connected to vinyl tubing (Dural Plastics, 0.5 mm inner diameter, 1.0 mm outer diameter), which exited at the back. Catheters were flushed before and after each training session with 0.1 ml of a saline solution containing 1.25 units per milliliter hep-

arin and 0.08 mg/ml gentamycin to prevent blood clotting and infection, respectively, at the tip of the catheter.

Apparatus

Operant chambers (30 cm by 24 cm by 29 cm, Coulbourn Instruments), enclosed individually in sound-attenuation chests, have been described in detail elsewhere (Schindler, Thorndike, & Goldberg, 1993). Each chamber had a metal grid floor and two nose-poke holes (activated by the breaking of a photobeam 0.5 cm inside the hole), one on each side of the right wall. Previous data indicated that, in the absence of differential reinforcement, neither hole is favored. A 4500-Hz 83-dB auditory stimulus (measured with a General Radio sound-level meter, on scale CS, 2.5 cm off the floor and 2.5 cm from the center of the front wall) was provided by a Sonalert (Model 628) operated at 8.75 V. A dim green lamp (Coulbourn Model E11-02) was illuminated throughout each session as a houselight. The visual stimulus (referred to as the ''light stimulus'' or simply ''light'' in the remainder of this paper, as opposed to the houselight, which was on throughout each session) was provided by a shielded 28-V white lightbulb (No. 1820) that produced 5.5 footcandles illumination (measured with Simpson Model 408-2 meter, pointed towards the light source, 2.5 cm off the floor and 2.5 cm from the center of the front wall). The Sonalert and white light were situated on the right wall (24 cm wide), above and between the nose-poke holes. Heroin (National Institute on Drug Abuse) was delivered through Tygon tubing wrapped in a metal spring, suspended through the ceiling from a single-channel fluid swivel. This tubing was attached to a syringe pump (MED Associates) using a 10-ml syringe. To reduce tension on the catheter, the spring was attached to a 20-mm plastic screw mounted on the rat's head at the time of catheter implantation. Self-administered heroin solution was delivered at a rate of 3.19 ml per minute over approximately 1 to 2 s, with the duration of the infusion adjusted according to body weight. The concentration of the heroin solution (in sterile 0.9% saline vehicle) was 0.33 mg/ml for the 0.1 and 0.05 mg/kg doses and 0.165 mg/ml for the 0.025 mg/kg dose. Experimental events were controlled by computer using a MED Associates software and interface system.

Procedure

Acquisition and discrimination training. Following implantation of catheters and 3 to 5 recovery days, self-administration training was begun. Nose poking for heroin was acquired without the use of a successive-approximation procedure or pretraining with food, which had been used in the analogous cocaine study (Panlilio et al., 1996). During acquisition sessions, rats were placed in the chamber for approximately 5 hr per day with the light stimulus present throughout the session. Each response in the left hole produced a 0.1 mg/kg infusion of heroin, which was accompanied by pulsing of the stimulus light at a rate of 10 Hz (alternating between on and off every 0.1 s) to provide immediate feedback for the reinforced response. The light continued to pulse for a total of 30 s (including 1 to 2 s infusion time), and responding had no scheduled consequences during this period (timeout). Responses in the right hole (inactive hole) were recorded throughout the session, but had no scheduled consequences at any time. During training and testing, response rates in the inactive hole were near zero for all rats and are therefore not reported here.

On Day 6, the unit dose of heroin was reduced to 0.05 mg/kg. On Day 7, the timeout was reduced to 10 s and a multiple schedule was introduced, under which light and no-light components alternated. In the presence of light, each left-hole response was reinforced. In the absence of light (the extinction component), no heroin was delivered. The duration of light components was scheduled to be 300 s, but the component ended earlier if no response occurred within 40 s after drug delivery. The occurrence of components ending due to the latter contingency was not recorded, but casual observation revealed that at least half of the VR components ended this way. Extinction components were scheduled to last 500 s. However, if responses occurred near the end of the component, a response-correction contingency extended this period so that the component did not end until at least 10 s had passed without a response. This differential-reinforcement-of-other-behavior

contingency was intended to reduce responding in the absence of tone and light.

Starting on Day 10, the following changes were made: (a) A VR schedule was instituted in the presence of light; (b) the session length was reduced to 3 hr; (c) the scheduled duration of the extinction component was reduced to 300 s; (d) the value of the VR was increased to three (range, one to seven responses) over three sessions; and (e) the response-correction value for the extinction component was increased to 20 s. On Day 13 the unit dose of heroin was reduced to 0.025 mg/kg, where it remained for the duration of the experiment. A similar dose of heroin (0.03 mg/kg) has been shown to maintain self-administration in rats without producing physical dependence (Dai, Corrigall, Coen, & Kalant, 1989), although shorter sessions (1.5 hr) were used in that study.

Training with the light stimulus was suspended and tone training was conducted on Days 17 through 22. A multiple schedule like the one used with light was in effect, except that the tone component was scheduled to be 500 s and the extinction component (no tone) was scheduled to be 300 s. The duration of these tone components was longer than the 300-s light components used earlier in training because the novelty of the tone (and possibly the absence of the light stimulus, which had already been established as a discriminative stimulus) initially disrupted self-administration responding. Like the light, the tone was pulsed at 10 Hz during infusion and timeout. The response correction value was increased to 30 s over 5 days.

Following discrimination training with the tone, a three-ply multiple schedule was instituted (Day 23), with a VR 3 contingency of heroin self-administration operating in tone and in light and extinction in the absence of tone and light. Tone and light components were separated by extinction components (absence of tone and light). Following an extinction component, there was an equal probability of entering a tone or a light component, with the stipulation that the same stimulus could not appear in more than three consecutive VR components. Components were scheduled to last 300 s, with the actual component durations affected by the same contingencies as in the earlier multiple schedules. Under this final training schedule, sessions lasted approximately 3 hr per day.

After at least three sessions under the three-ply multiple schedule, training continued until the response rates in light and tone were at least seven times greater than those in extinction, with separate rates calculated for postlight and posttone extinction components. Once this training criterion was met, a stimulus-compounding test was given in extinction the next day. (Rat 96 was maintained on the baseline schedule for 1 additional day after meeting this criterion because of an unusually high rate of postlight responding during the session prior to meeting criterion.)

Stimulus-compounding test performed in extinction. Immediately prior to testing, the baseline training schedule was in effect for a 30-min warm-up period. During the test there were 12 presentations of each of the three test stimuli (tone, light, and tone–light). Each test-stimulus presentation lasted 60 s and was followed by the absence of tone and light for 60 s. The order of these 36 stimulus presentations was organized in blocks of three, with each stimulus occurring once in each block. The order of the presentations was determined by four Latin squares, so that each stimulus (tone, light, and tone–light) followed each of the other stimuli an equal number of times. Responding had no scheduled effect during the test, which lasted 72 min.

Maintenance test. Following the first compounding test, the rats were returned to the three-ply multiple-schedule baseline for at least two sessions. Then, after again meeting the 7:1 discrimination criterion described for the extinction test, they were given a stimulus-compounding test under maintenance conditions. During the maintenance test, heroin was made available on a fixed-ratio (FR) 3 schedule during all test-stimulus presentations (tone, light, and compound). The procedure for this test was the same as that used earlier for maintenance testing with cocaine (Panlilio et al., 1996). An FR schedule was used during testing to avoid any potential bias due to the variability of reinforcement under a VR schedule. For example, if a VR schedule were used during testing, three responses might produce three heroin infusions in one component but none in another component. As during training, the pulsed

light or tone was presented during infusion and for 10 s following each infusion. During infusion and timeout in compound-stimulus trials, tone and light were pulsed together. Tone, light, and tone–light were presented six times each, with each presentation lasting 60 s (not including timeout periods). These 18 test-stimulus presentations were organized in blocks, with each stimulus occurring once in each block and the order determined by two Latin squares. Test stimuli were separated by 300-s periods of extinction (absence of tone and light), in which responding had no scheduled effect. Thus, the test lasted 108 min plus 10 s for each infusion during the test.

RESULTS

Training

Training data for each rat are presented in Figure 1. Self-administration was acquired rapidly; although rates of intake were relatively low (2.4 to 5.4 infusions per hour), they were stable during each 5-hr session for the first 4 days. Response rates of each rat increased when the unit dose was reduced from 0.1 to 0.05 mg/kg on Day 6, and these rates continued to increase during light discrimination training. All rats exhibited a light versus no-light discrimination by the end of light training (Day 16). Institution of tone training disrupted responding for the first two sessions (Days 17 and 18), but the tone discrimination became evident in all rats by the third tone session (Day 19).

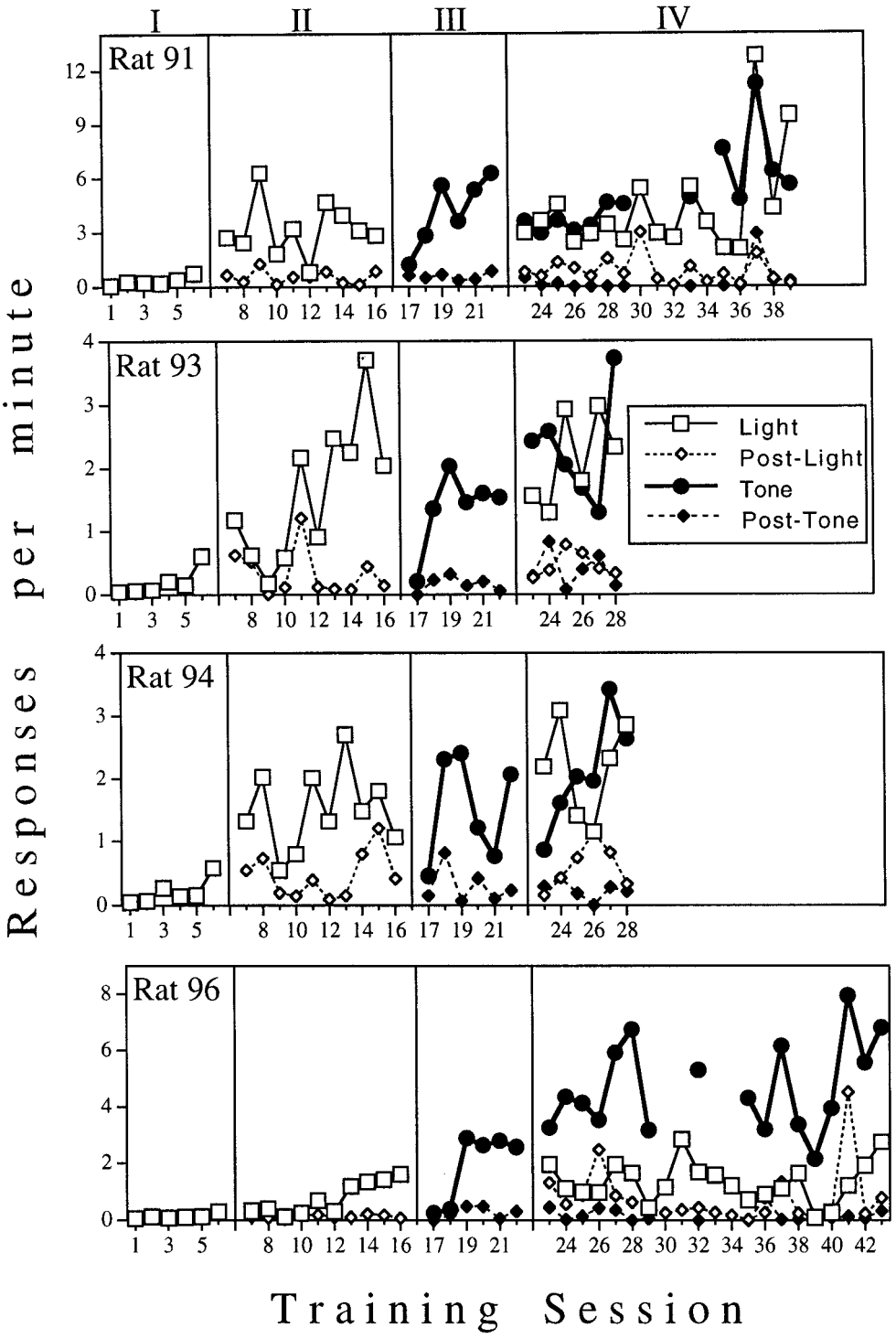
During training with the three-ply multiple schedule (starting on Day 23), there was a tendency for the auditory discrimination performance to be better than the visual. For this reason, Rats 91 and 96 were trained for several sessions without the tone during this phase to give them extra practice with the light (see interruptions in ''tone'' and ''post-tone'' lines for these rats in Figure 1). By the time they met the 7:1 discrimination criterion, all rats tended to initiate responding soon after the tone or light was presented. Baseline response rates in the present study ($M \pm SEM$: 3.1 ± 0.4 responses per minute in light and 4.9 ± 1.0 in tone) were similar to those in the analogous cocaine study (5.3 ± 0.9 in light and 4.5 ± 0.6 in tone; Panlilio et al., 1996). Performances remained stable during the baseline sessions between the two stimulus-compounding tests (not shown).

Compounding Test Performed in Extinction

During the extinction test (see Figure 2), the tone–light compound controlled higher rates of responding than either tone or light alone in every subject. The total number of test responses in the presence of tone, light, and the tone–light compound during the extinction test differed significantly in a repeated measures analysis of variance, $F(2, 6) = 12.51$, $p < .01$. The compound controlled more responding than either tone, $F(1, 6) = 18.08$, $p < .01$, or light, $F(1, 6) = 19.43$, $p < .01$. Levels of tone and light responding did not differ from each other, $F(1, 6) = 0.02$, $p > .8$. The tone and light discriminations were not disrupted during extinction, with response rates in the absence of tone and light (indicated in parentheses in Figure 2) remaining low during testing.

Maintenance Test

Compounding of tone and light increased both response rates and heroin intake rates for each rat during the maintenance test (see Figure 3). The total number of infusions in tone, light, and the tone–light compound differed significantly, $F(2, 6) = 8.67$, $p < .02$. The compound controlled higher rates of intake than either tone, $F(1, 6) = 11.67$, $p < .02$, or light, $F(1, 6) = 14.22$, $p < .01$. Rates in the presence of tone and light did not differ from each other, $F(1, 6) = 0.13$, $p > .7$. Few responses were emitted in the absence of tone and light. On average, heroin was self-administered during stimulus compounding at approximately twice the rates in tone or light alone (see center panel of Figure 3). Furthermore, infusion rates in the presence of the tone–light compound were substantially higher than the baseline rates during training (final three sessions) in 3 rats (see lower panel of Figure 3). Although the intake rates in tone and light alone during testing were lower than baseline for Rat 94, the compound stimulus still produced a clear increase in drug intake relative to tone or light alone during testing.


I
II
III
IV
Rat 91
Rat 93
Rat 94
Rat 96
Light
Post-Light
Tone
Post-Tone
Responses per minute
Training Session

DISCUSSION

When heroin was made available only in the presence of specific stimuli, the stimuli acquired discriminative control of self-administration responding. When these discriminative stimuli were presented in compound, they controlled response rates that were significantly higher than when they were presented separately. During extinction tests, when ''drug seeking'' was measured in the absence of drug delivery, compounding increased responding approximately threefold. When drug availability was maintained during testing, compounding increased both responding and drug intake approximately twofold.

The magnitude of these effects closely matched those obtained earlier with cocaine, when stimulus compounding also tripled responding during extinction testing and doubled drug intake during maintenance testing (Panlilio et al., 1996). For comparison, Figures 4 and 5 present the extinction and maintenance test results, respectively, of the individual subjects trained with cocaine in the earlier study. These data, which were presented only as group means in the earlier paper, are similar to those obtained with heroin in the extinction and maintenance tests of the present study (seen in Figures 2 and 3, respectively). Although the total number of test responses during extinction testing was higher in the cocaine study, the patterns of the individual results were consistent both within and between the heroin and cocaine studies. That is, the proportionality between response rates controlled by the tone, light, and tone–light were similar in all subjects. When the extinction-test results were expressed as percentages (to adjust for differences in overall rate), the slopes and variability of the cumulative curves for heroin and cocaine were almost identical (cf. lower right graphs of Figures 2 and 4). During maintenance testing, the enhanced rates of responding and drug intake with heroin were similar to those with cocaine (cf. Figures 3 and 5).

This close correspondence of results was obtained despite several procedural differences between the heroin and cocaine studies: (a) use of a nose-poke response with heroin and lever pressing with cocaine; (b) use of active and inactive nose-poke holes to control for nonspecific locomotor activation during testing in the heroin study; (c) acquisition of self-administration without food pretraining in the heroin study; (d) use of auditory and visual stimuli with different characteristics; and (e) stimulus-compound testing in extinction without reacquisition periods in the heroin study. Because heroin self-administration was acquired without food pretraining, it seems unlikely that the food training used to shape lever pressing in the earlier cocaine study affected the outcome of the stimulus-compounding tests. Similarly, the use of reacquisition periods during extinction testing in the cocaine study may have increased the total number of test responses, but it does not seem to have affected the pattern of the test results.

Over the course of training with heroin, variables such as the dose of the drug and the duration of components were manipulated to obtain moderate rates of responding in the presence of the tone and the light, which would allow either increases or decreases in rate during stimulus-compounding tests. A consistent finding from a large number of stimulus-compounding studies (reviewed by Weiss, 1978) is that the absolute rate controlled by the individual stimuli is not as im-

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Fig. 1. Response rates (responses per minute) during each training session for each rat in the present study. Acquisition of heroin self-administration in the presence of light (shown in Panel 1) was followed by light versus no-light discrimination training (Panel 2), tone versus no-tone discrimination training (Panel 3), and finally by three-ply multiple schedule training (Panel 4). Under the three-ply schedule, responding was reinforced with 0.025 mg/kg heroin on a VR 3 schedule in tone and in light. Responding in the absence of tone and light was not reinforced. Response rates in the absence of tone and light are shown separately for posttone and postlight components. Training under the three-ply schedule was continued until response rates in tone and in light were at least seven times greater than in the posttone and postlight components, respectively. This criterion was met on the last day shown for all rats, and a stimulus compounding test was performed in extinction on the next day. Although Rat 96 first met the criterion on Day 42, training was continued for 1 extra day (during which the criterion was again met) for this rat because of unusually high postlight rates on Day 41. Note that the scale of the *y* axis differs across rats.

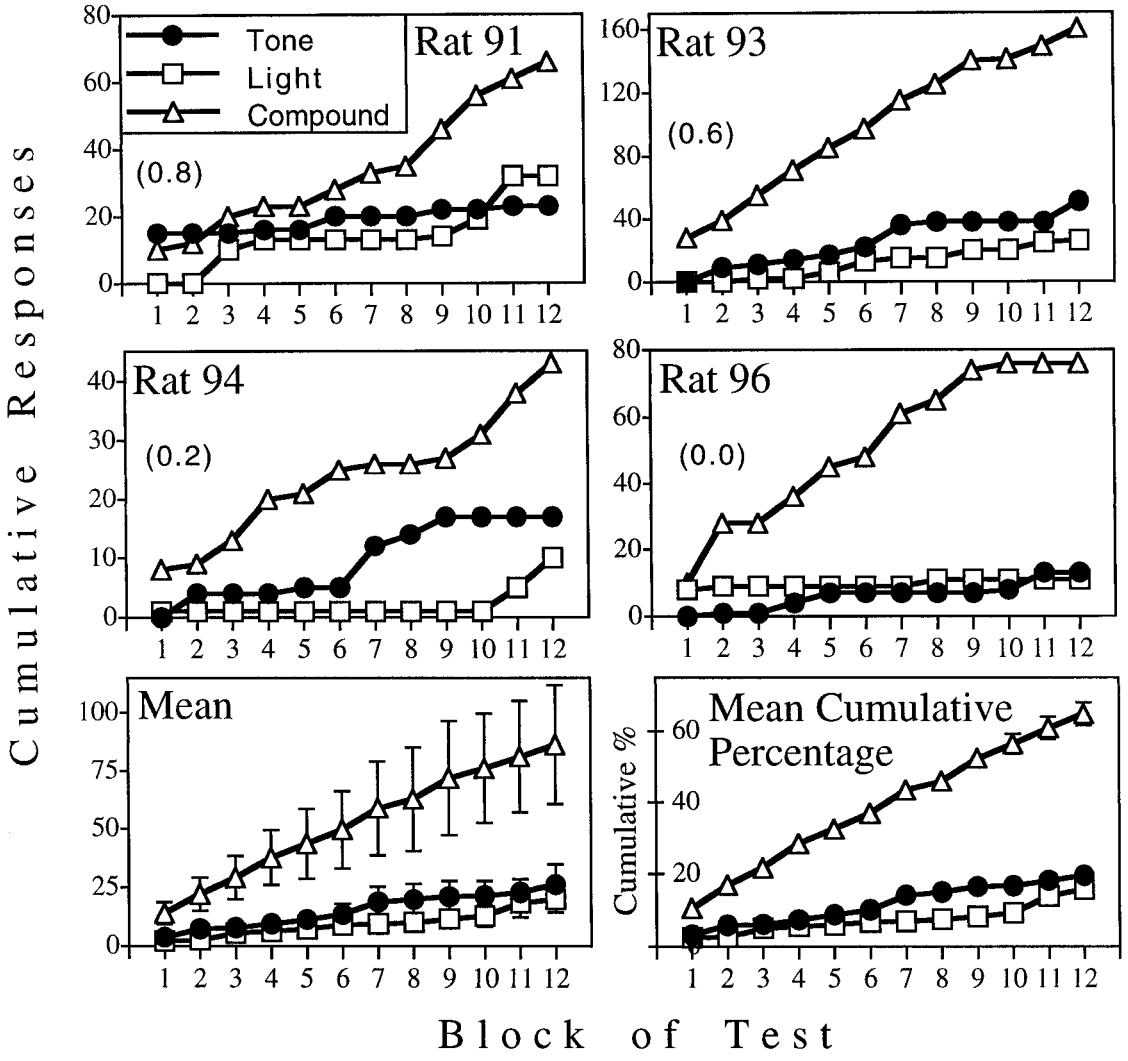

Fig. 2. Cumulative response curves for each rat in the present study during the stimulus-compounding test performed in extinction. Group means (± *SEM*) are shown in lower left graph as cumulative responses and in the lower right graph as cumulative percentages of total test responses emitted in tone, light, and tone–light. Cumulative percentages were calculated separately for each rat, then averaged. Error bars not visible in mean figures are covered by plotted symbols. During each block of testing, tone, light, and tone–light periods lasted 1 min each, and the absence of tone and light lasted a total of 3 min. The mean response rate (responses per minute) in the absence of tone and light during testing is presented in parentheses for each rat. Note that the scale of the *y* axis differs across rats.

portant as the *change* in response rate they control relative to their absence. To produce response-enhancement effects during compounding, the individual stimuli must control increases in responding relative to their absence. Thus, the generality of the results obtained under the present conditions should not be to limited to the specific dose and other parameters used here, but should apply to any set of conditions in which the individual stimuli are (a) discriminative for increased responding and (b) differentially associated with delivery of heroin.

Stimuli that have been associated with cocaine (Barr et al., 1983; Bridger, Schiff, Cooper, Paredes, & Barr, 1982; Panlilio & Schindler, 1997) or opioid (Walter & Kuschinsky, 1989) administration can sometimes elicit

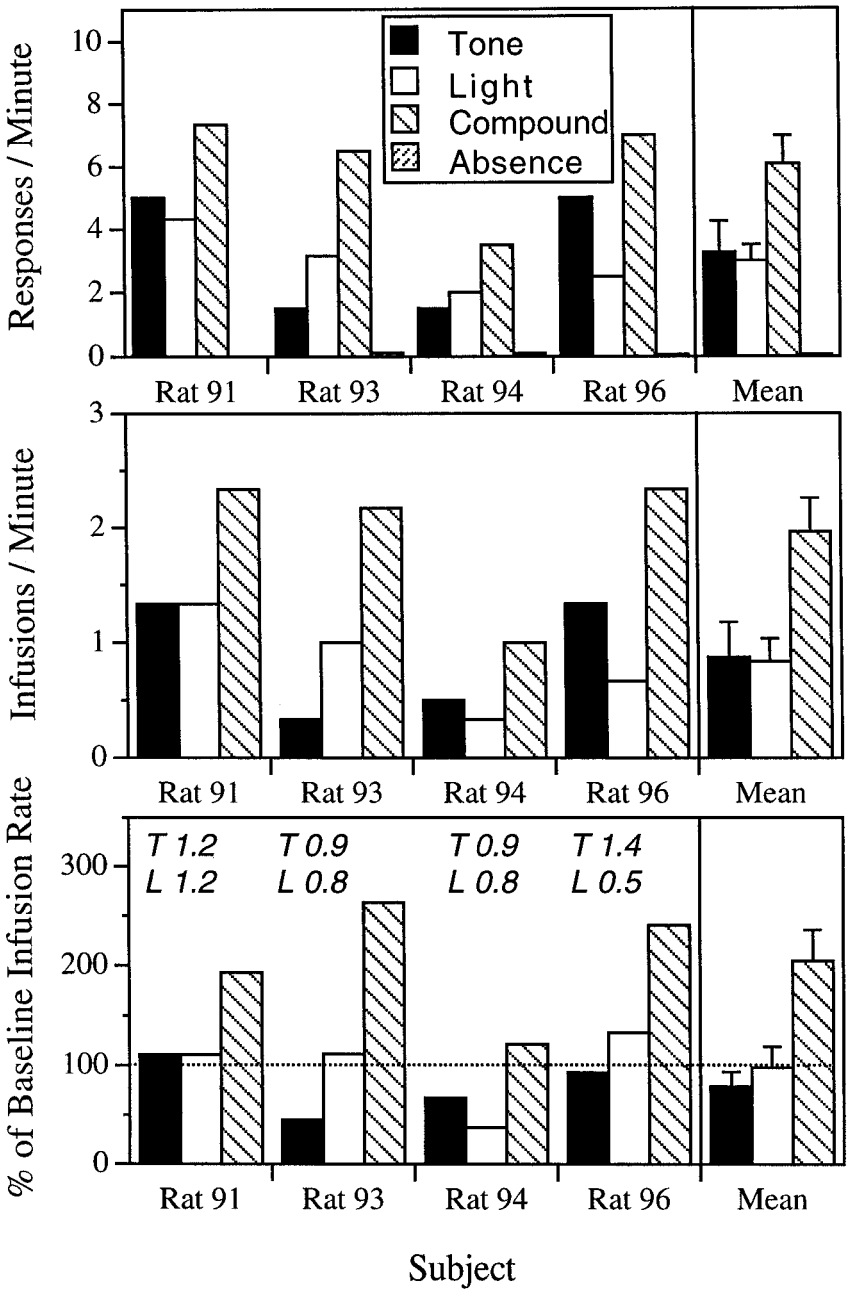

Fig. 3. Response rates and infusion rates in the presence of tone, light, and the tone–light compound during the stimulus-compounding test performed under maintenance conditions for each rat in the present study. Group means (± *SEM*) are shown in the right panel of each graph. Upper graph shows absolute response rates (responses per minute), including rates in the absence of tone and light. Center graph shows absolute rates of infusion (infusions per minute), and lower graph shows rates of infusion during the test as a percentage of baseline infusion rates during the three training sessions prior to testing. The percentage for tone–light was calculated using the mean of the tone and light rates during the final three training sessions. The baseline rates in the presence of tone (T) and light (L) are indicated numerically for each rat.

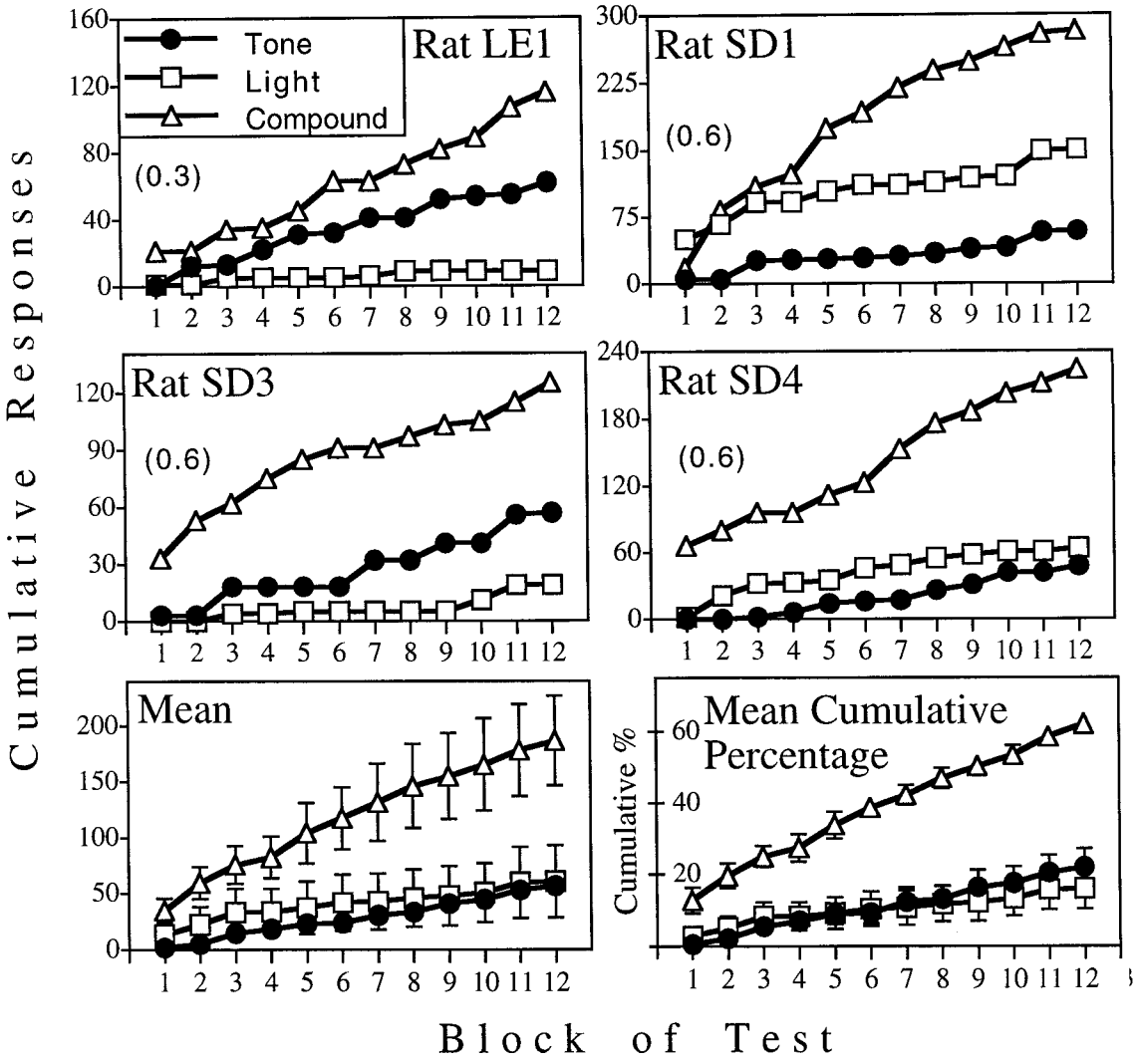

Fig. 4. Cumulative response curves during a stimulus-compounding test performed in extinction for rats trained with cocaine in the study of Panlilio et al. (1996). These results are from the "differential" group of the cocaine experiment, for which the training and testing procedures were most similar to those used with heroin in the present study. Group means (± *SEM*) are shown in lower left graph as cumulative responses and in the lower right graph as cumulative percentages of total test responses in tone, light, and tone–light. Cumulative percentages were calculated separately for each rat, then averaged. Error bars not visible in mean figures are covered by plotted symbols. During each block of testing, tone, light, and tone–light periods lasted 1 min each, and the absence of tone and light lasted a total of 3 min. The mean response rate in the absence of tone and light during testing is presented in parentheses for each rat. Note that the scale of the *y* axis differs across rats.

general locomotor activity. Such conditioned activity could conceivably contribute to stimulus-compounding effects like those in the present study by causing "accidental" contact with the lever or nose-poke hole. However, such incidental responding would be expected to occur in both the active and inactive nose-poke holes. Inactive-hole responses were extremely rare during training with heroin and did not increase during testing. Although conditioned activity can be elicited by long-duration auditory and visual stimuli associated with intraperitoneal cocaine administration (Panlilio & Schindler, 1997), such conditioning has never been demonstrated with relatively brief stimulus presentations

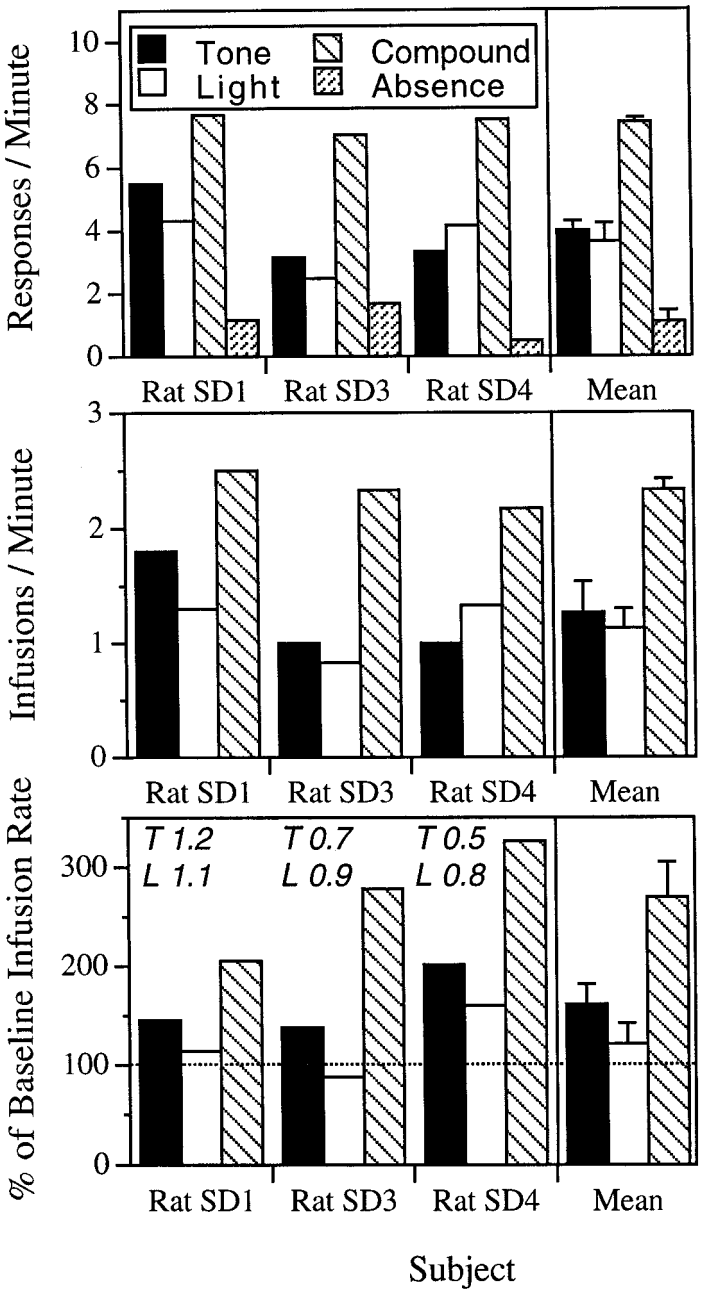

Fig. 5. Response rates and infusion rates in the presence of tone, light, and the tone–light compound during the stimulus-compounding test performed under maintenance conditions for rats trained with cocaine in the study of Panlilio et al. (1996). Group means (± *SEM*) are shown in the right panel of each graph. Upper graph shows absolute response rates (responses per minute), including rates in the absence of tone and light. Center graph shows absolute rates of infusions (infusions per minute), and lower graph shows rates of infusion during the test as a percentage of baseline infusion rates during the three training sessions prior to testing. The percentage for tone–light was calculated using the mean of the tone and light rates during the final three training sessions. The baseline rates in the presence of tone (T) and light (L) are presented numerically for each rat. Note that only 3 subjects received this maintenance test because Rat LE1, which received the extinction test as shown in Figure 4, died before the maintenance test could be performed.

(lasting less than 5 min) that alternate repeatedly, such as in the multiple schedule used here. Furthermore, although the behavioral baselines were not directly comparable, the increases in activity (approximately 25%) produced by long cocaine-paired stimuli (Panlilio & Schindler, 1997) were much smaller than the increases in operant responding (approximately 200%) observed during stimulus compounding in the present study and the analogous cocaine study (Panlilio et al., 1996). Additional evidence that cocaine-associated stimuli do not enhance operant responding by producing incidental responses comes from recent studies of response-independent cocaine administration. When exteroceptive stimuli were paired with experimenter-delivered intravenous cocaine on a baseline of food-reinforced nose poking, the stimuli suppressed responding rather than enhancing it (Panlilio, Weiss, & Schindler, in press; Schindler, Thorndike, Ma, & Goldberg, 2000).

The evidence described above suggests that incidental responding due to conditioned increases in general locomotor activity did not contribute to the response enhancements observed during stimulus compounding in the present study and the analogous cocaine study (Panlilio et al., 1996). However, locomotor activation may be just one manifestation of a classically conditioned motivational effect (e.g., see Pert, 1994) that has been shown to profoundly influence operant responding and the outcome of stimulus-compounding tests. This phenomenon is *incentive-motivation* (Bindra, 1972; Weiss, 1978), a process by which conditioned stimuli can acquire the ability to energize operant behavior. For example, current accounts of drug craving contend that drug-associated stimuli can not only become conditioned reinforcers but can also increase the motivation to seek and consume drugs of abuse (Markou et al., 1993; Robinson & Berridge, 1993).

Conditioning of incentive-motivation was demonstrated in a series of stimulus-compounding experiments performed with food reinforcement (Weiss, 1978; Weiss & Schindler, 1987, 1989). In three groups of rats, tone and light were each established as discriminative stimuli that controlled moderate rates of lever pressing. In the absence of tone and light, responding essentially ceased. The incentive-motivational properties conditioned to the tone and light during training were manipulated by varying the frequency of food reinforcement received in their presence (100%, 50%, or 0%) relative to their absence. When tone and light were compounded, a range of response-enhancement effects was obtained. The magnitude of these effects varied as a direct function of the incentive-motivational value conditioned to the tone and light during training. The largest increases (approximately threefold) occurred when 100% of reinforcers had been received in the presence of the tone and the light—a condition in which the stimuli should have acquired excitatory incentive-motivational value. When the rates of reinforcement in the presence and absence of the stimuli were equal during training (in the 50% condition)—when the stimuli should have acquired neutral incentive-motivational value—responding was doubled during compounding. This doubling can be considered a ''pure'' product of the discriminative control (as opposed to motivational effects) exerted by the compounded stimuli. When all reinforcement was received in the absence of the stimuli (in the 0% condition)—when the stimuli should have inhibited incentive-motivation—compounding did not enhance responding. Thus, inhibition of incentive-motivation in this 0% group prevented the increase produced by purely operant, discriminative factors in the 50% group.

In all three of the food-trained groups described above, the baseline lever-pressing performances (controlled by tone, light, and their absence) were indistinguishable during training. Nevertheless, stimulus compounding produced a range of response-enhancement effects during testing, and these effects varied as a function of the incentive-motivational values conditioned to the individual stimuli (excitatory, neutral, or inhibitory). In light of this fact, it is striking that the magnitude of the response-enhancement effect seen with food reinforcement in the 100% condition described above was similar to that obtained in analogous 100% groups trained with heroin (present study), cocaine (Panlilio et al., 1996), water (Weiss et al., 1988), shock avoidance (Emurian & Weiss, 1972; Weiss, 1976), and also with morphine in 2 rats trained in a pilot study for the present ex-

periment. The consistency of these results suggests that the effects of stimulus compounding on drug self-administration reflect the influence of the incentive-motivation properties conditioned to the training stimuli. Thus, stimulus compounding may provide a productive means of investigating incentive-motivation, which has been suggested to be an underlying mechanism of drug craving (Markou et al., 1993; Pert, 1994; Robinson & Berridge, 1993).

Conclusion

Although heroin and cocaine both function as positive reinforcers, and as such may activate neural pathways common to all positive reinforcers, they also have actions that distinguish them from one another (Wise, 1996). Despite any inherent differences between the pharmacological and behavioral effects of these drug reinforcers, heroin and cocaine clearly produce similar effects in the stimulus-compounding paradigm. Robust enhancements of responding were observed in each subject tested in the present heroin study and in the analogous cocaine study (Panlilio et al., 1996). The consistency of these enhancements across reinforcers and training procedures indicates that they involve a fundamental and general mechanism of learning and behavior. The results obtained under maintenance conditions show that this environmentally induced enhancement can at least temporarily override the mechanisms by which animals typically regulate their levels of drug intake (e.g., as seen with cocaine in the study by Dougherty & Pickens, 1976; and with heroin in the study by Wise, Leone, Rivest, & Leeb, 1995). Thus, the compounding of drug-related stimuli may model one mechanism by which human drug taking escalates from controlled, casual use to ''uncontrollable'' abuse.

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